General

Guideline Title

The management of women with red cell antibodies during pregnancy.

Bibliographic Source(s)

Royal College of Obstetricians and Gynaecologists (RCOG). The management of women with red cell antibodies during pregnancy. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2014 May. 26 p. (Green-top guideline; no. 65). [42 references]

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

In addition to these evidence-based recommendations, the guideline development group also identifies points of best clinical practice in the original guideline document.

Classification of evidence levels (1++ to 4) and grades of recommendations (A–D) are defined at the end of the "Major Recommendations" field.

Red Cell Antibodies in Pregnancy

What Red Cell Antibodies Are Clinically Significant (Maternal and Fetal) During Pregnancy?

D - All women should have their blood group and antibody status determined at booking and at 28 weeks of gestation (see Appendix 2 in the original guideline document).

What Are the Implications for the Fetus and Neonate from Red Cell Antibodies?

D - Clinicians should be aware that severe fetal anaemia can result in hydrops which significantly worsens the perinatal outcome.

When and How Should Paternal and Fetal Genotyping Be Performed?

C - Non-invasive fetal genotyping using maternal blood is now possible for D, C, c, E, e and K antigens. This should be performed in the first instance for the relevant antigen when maternal red cell antibodies are present.

Is Karyotyping Contraindicated in the Presence of Maternal Red Cell Antibodies?

D - Anti-D prophylaxis should be given to cover invasive testing if the mother is rhesus D (RhD) negative and is not sensitised.

If the Fetus Is at Risk of Anaemia, When Should Referral to a Fetal Medicine Specialist Take Place?

D - For antibodies other than anti-D, anti-c and anti-K, the following should prompt referral to a fetal medicine specialist: a history of previous significant haemolytic disease of the fetus and newborn (HDFN) or intrauterine transfusion (IUT), or a titre of 32 or above, especially if the titre is rising as rising titres correlate with increasing risk and severity of anaemia.

What Thresholds Should Be Used for the Various Antibodies that Could Cause Fetal Anaemia to Trigger Referral for Further Investigation or Monitoring?

C - An anti-D level of >4 iu/ml but <15 iu/ml correlates with a moderate risk of HDFN and an anti-D level of >15 iu/ml can cause severe HDFN. Referral for a fetal medicine opinion should therefore be made once anti-D levels are >4 iu/ml.

C - An anti-c level of >7.5 iu/ml but <20 iu/ml correlates with a moderate risk of HDFN, whereas an anti-c level of >20 iu/ml correlates with a high risk of HDFN. Referral for a fetal medicine opinion should therefore be made once anti-c levels are >7.5 iu/ml.

Once Detected How Often Should Antibody Levels Be Monitored During Pregnancy?

D - Anti-D and anti-c levels should be measured every 4 weeks up to 28 weeks of gestation and then every 2 weeks until delivery.

D - Although anti-K titres do not correlate well with either the development or severity of fetal anaemia, titres should nevertheless be measured every 4 weeks up to 28 weeks of gestation, then every 2 weeks until delivery.

How Should Pregnancies at Risk of Fetal Anaemia Be Monitored?

B - If the fetus carries the corresponding antigen for a maternal antibody which is capable of causing fetal anaemia and if the antibody levels/titres rise beyond the levels detailed in Section 6.7 in the original guideline document then the pregnancy should be monitored weekly by ultrasound, specifically assessing the fetal middle cerebral artery peak systolic velocities (MCA PSV).

If Fetal Transfusion Is Required What Type of Donor Blood Should Be Used?

D - Red cell preparations for IUT should be group O (low titre haemolysin) or ABO identical with the fetus (if known) and negative for the antigen(s) corresponding to maternal red cell antibodies.

If Maternal Transfusion Is Required, What Type of Donor Blood or Blood Components Should Be Used?

D - Red cell components of the same ABO group and RhD type, and that are K negative and cytomegalovirus (CMV) negative, should be selected.

Should RhD-Negative Women Who Have Anti-D or Non-Anti-D Antibodies Receive Routine Antenatal or Postnatal Prophylaxis?

B - Anti-D immunoglobulin should be given to RhD-negative women with non-anti-D antibodies for routine antenatal prophylaxis, for potential antenatal sensitising events and postnatal prophylaxis.

D - If immune anti-D is detected, prophylaxis is no longer necessary.

D - Discussion and liaison with the transfusion laboratory are essential in determining whether anti-D antibodies are immune or passive in women who have previously received anti-D prophylaxis.

Requirements for Blood

What Are the Logistics of Obtaining Blood or Blood Components for the Woman, Fetus or Neonate?

Blood for IUT

D - Clinicians should be aware that blood for IUT has the same requirements as blood for neonatal exchange (see Section 7.1.3 in the original guideline document), except that plasma is removed by the blood centre to increase the haematocrit to 0.70 to 0.85 and it is always irradiated.

Blood for Neonatal Exchange

D - Blood should be ABO compatible with the neonate and mother (to avoid ABO HDFN from the woman's anti-A or -B antibodies present), RhD negative (or RhD identical with neonate), K negative, negative for the corresponding antigen to which the woman has an antibody and cross-match compatible with the woman's blood sample.

D - Blood should be less than 5 days old (to ensure low supernatant potassium levels), CMV negative and irradiated unless the risk to the baby of delaying exchange transfusion while obtaining irradiated blood outweighs this. It should be plasma reduced (rather than in saline-adenine-glucose-mannitol [SAGM] additive solution), with a haematocrit of 0.50 to 0.60.

Blood for Neonatal Small Volume ('Top-up') Transfusion

D - Blood should be ABO compatible with the neonate and mother (to avoid ABO HDFN from the woman's anti-A or -B antibodies present), RhD negative (or RhD identical with neonate), K negative and negative for the corresponding antigen to which the woman has an antibody and cross-match compatible with the woman's blood sample.

D - Blood should be CMV negative but does not need to be irradiated unless the neonate has had a previous IUT and blood can be stored in SAGM (rather than plasma reduced) and be up to 35 days old (as a top-up transfusion is a much smaller volume than an exchange transfusion).

D - Clinicians considering transfusion in a neonate must check if the baby has had an IUT, as if so, blood must be irradiated to prevent transfusion-associated graft-versus-host disease.

Management

How Should the Neonate Be Managed?

C - This depends on the risk of haemolysis or anaemia conferred by the relevant red cell antibody. The neonate should have regular clinical assessment of its neurobehavioural state and be observed for the development of jaundice and/or anaemia.

C - Clinicians should be aware that if bilirubin levels rise rapidly or above the interventional threshold, phototherapy and/or exchange transfusion may be required.

Long-Term Consequences of Red Cell Antibodies to Women and Their Offspring

What Are the Long-Term Health Concerns for the Children of Women with Red Cell Antibodies During Pregnancy?

C - Clinicians should be aware that some infants may experience anaemia persisting for a few weeks following birth.

C - Clinicians should be aware that some infants may develop late anaemia which is usually due to hyporegenerative anaemia.

Definitions:

Classification of Evidence Levels

1++ High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias

1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias

1– Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias

2++ High-quality systematic reviews of case-control or cohort studies or high-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal

2+ Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

2- Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal

3 Non-analytical studies, e.g., case reports, case series

4 Expert opinion

Grades of Recommendations

A – At least one meta-analysis, systematic review or randomised controlled trial rated as 1++ and directly applicable to the target population; *or*

A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results

B – A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of

results; *or*

Extrapolated evidence from studies rated as 1++ or 1+

C – A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 2++

D – Evidence level 3 or 4; *or*

Extrapolated evidence from studies rated as 2+

Clinical Algorithm(s)

The following algorithms are provided in the original guideline document:

- Timing and frequency of antibody screening in pregnancy
- Management algorithm for pregnancies complicated with anti-D, anti-K or anti-c alloimmunisation

Scope

Disease/Condition(s)

Red cell antibodies during pregnancy

Note: The guideline does not address the management of the pregnant woman with anti-platelet antibodies or other autoimmune or alloimmune antibodies.

Guideline Category

Diagnosis

Evaluation

Management

Risk Assessment

Screening

Treatment

Clinical Specialty

Obstetrics and Gynecology

Pediatrics

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

- To provide guidance on the management of pregnant women with red cell antibodies predating the pregnancy or those developing antibodies during pregnancy
- To provide guidance on the management of fetal anaemia caused by red cell antibodies, as well as the early management of the neonate at risk of anaemia and/or hyperbilirubinaemia

Target Population

Pregnant women and newborn infants

Interventions and Practices Considered

1. Detection of red cell antibodies in pregnancy
    - Blood group and antibody status
    - Non-invasive fetal genotyping
2. Anti-D prophylaxis
3. Referral to a fetal medicine specialist
4. Monitoring
    - Measurement of anti-D and anti-C levels
    - Ultrasound
    - Detection of anti-K antibodies
5. Maternal, neonate and intrauterine transfusion (IUT)
    - Red cell components of the same ABO group and rhesus D (RhD) type
    - K negative and cytomegalovirus (CMV) negative
6. Management of neonate
    - Regular clinical assessment
    - Observation for jaundice or anaemia
    - Phototherapy and/or exchange transfusion if bilirubin levels rise rapidly

Major Outcomes Considered

- Sensitivity and specificity of diagnostic tests
- Pregnancy outcomes of women referred for antenatal fetal therapy for fetal anaemia
- Perinatal morbidity and mortality

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

This Royal College of Obstetricians and Gynecologists (RCOG) guideline was developed in accordance with standard methodology for producing RCOG Green-top Guidelines. The Cochrane Library (including the Cochrane Database of Systematic Reviews), DARE, EMBASE, TRIP, MEDLINE and PubMed (electronic databases) were searched for relevant randomised controlled trials, systematic reviews, meta-analyses and

other studies. The search was restricted to articles published between 1960 and July 2013. The databases were searched using the relevant Medical Subject Headings (MeSH) terms, including all subheadings, and this was combined with a keyword search. Search terms included: red cell antibody, red blood cell antigen, erythroblastosis fetalis, blood group incompatibility, haemolytic disease of newborn, anti-D, anti-c, anti-E, anti-K, Kidd, Duffy, Diego alloimmunisation. The search was limited to humans and the English language. National Health Service (NHS) Evidence and the National Guideline Clearinghouse (NGC) were also searched for relevant guidelines and reviews.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Classification of Evidence Levels

1++ High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias

1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias

1– Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias

2++ High-quality systematic reviews of case-control or cohort studies or high-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal

2+ Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

2– Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal

3 Non-analytical studies (e.g., case reports, case series)

4 Expert opinion

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

Reviewing and Grading of Evidence

Once the evidence has been collated for each clinical question it needs to be appraised and reviewed (refer to section 3 in "Development of RCOG Green-top guidelines: producing a clinical practice guideline" for information on the formulation of the clinical questions; see the "Availability of Companion Documents" field). For each question, the study type with least chance of bias should be used. If available, randomised controlled trials (RCTs) of suitable size and quality should be used in preference to observational data. This may vary depending on the outcome being examined.

The level of evidence and the grade of the recommendations used in this guideline originate from the guidance by the Scottish Intercollegiate Guidelines Network (SIGN) Grading Review Group, which incorporates formal assessment of the methodological quality, quantity, consistency, and applicability of the evidence base. The methods used to appraise individual study types are available from the SIGN Web site (www.sign.ac.uk/methodology/checklists.html). An objective appraisal of study quality is essential, but paired reviewing by guideline leads may be impractical because of resource constraints.

Once evidence has been collated and appraised, it can be graded. A judgement on the quality of the evidence will be necessary using the grading system (see the "Rating Scheme for the Strength of the Evidence" field). Where evidence is felt to warrant 'down-grading', for whatever reason, the rationale must be stated. Evidence judged to be of poor quality can be excluded. Any study with a high chance of bias (either 1– or 2–) will be excluded from the guideline and recommendations will not be based on this evidence. This prevents recommendations being based on poor-quality RCTs when higher-quality observational evidence is available.

Methods Used to Formulate the Recommendations

Expert Consensus

Informal Consensus

Description of Methods Used to Formulate the Recommendations

Guideline Development

The development of guidelines involves more than the collation and reviewing of evidence. Even with high-quality data from systematic reviews of randomised controlled trials, a value judgement is needed when comparing one therapy with another. This will therefore introduce the need for consensus.

Royal College of Obstetricians and Gynaecologists (RCOG) Green-top guidelines are drafted by nominated developers, in contrast to other guideline groups such as the National Institute for Health and Care Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN), who use larger guideline development groups. Equally, in contrast to other guideline groups, the topics chosen for development as Green-top guidelines are concise enough to allow development by a smaller group of individuals.

In agreeing the precise wording of evidence-based guideline recommendations and in developing consensus-based 'good practice points', the Guidelines Committee (GC) will employ an informal consensus approach through group discussion. In line with current methodologies, the entire development process will follow strict guidance and be both transparent and robust. The RCOG acknowledges that formal consensus methods have been described, but these require further evaluation in the context of clinical guideline development. It is envisaged that this will not detract from the rigor of the process but prevent undue delays in development.

Rating Scheme for the Strength of the Recommendations

Grades of Recommendations

A – At least one meta-analysis, systematic review or randomised controlled trial rated as 1++ and directly applicable to the target population; *or*

A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results

B – A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 1++ or 1+

C – A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 2++

D – Evidence level 3 or 4; *or*

Extrapolated evidence from studies rated as 2+

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Following discussion in the Guidelines Committee (GC), each Green-top guideline is formally peer reviewed. At the same time, the draft guideline is published on the Royal College of Obstetricians and Gynaecologists (RCOG) Web site for further peer discussion before final publication.

All comments will be collated by the RCOG and tabulated for consideration by the guideline leads. Each comment will require discussion. Where comments are rejected then justification will need to be made. Following this review, the document will be updated and the GC will then review the revised draft and the table of comments.

Once the GC signs-off on the guideline, it is submitted to the Standards Board for approval before final publication.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate management of women with red cell antibodies during pregnancy

Potential Harms

- Non-invasive genotyping is not possible for some red cell antigens. In these cases invasive testing (chorionic villus sampling [CVS] or amniocentesis) may be considered. However, the risks of the procedure (miscarriage, worsening of alloimmunisation) need to be balanced against the benefit that knowledge of the fetal genotype brings to the management of the pregnancy.
- The risks and benefits of intrauterine transfusion (IUT) should always be discussed with the woman who should be made aware of the consequences of untreated severe fetal anaemia (i.e. hydrops, preterm birth, perinatal death, severe neonatal jaundice and kernicterus) as well as the risks of neonatal exchange transfusion.
- The decision to use ABO-, rhesus D (RhD-) and K-compatible blood that is not matched for other antibodies (or O negative, where the woman's ABO and RhD groups are unknown) should be made on the balance of risks (severe haemorrhage versus a haemolytic transfusion reaction).
- Once referral to a fetal medicine specialist has been made for assessment of pregnancy at moderate or high risk of haemolytic disease of the fetus and newborn (HDFN), the value of subsequent quantitation of anti-D and anti-c levels is doubtful. Further testing is however required at 28 weeks for the development of additional red cell antibodies. Caution is required however if there is a history of a severely affected previous pregnancy even if the antibody levels are low in the current pregnancy.
- Middle cerebral artery peak systolic velocities (MCA PSV) monitoring is predictive of moderate or severe fetal anaemia with 100% sensitivity and a false positive rate of 12%. Monitoring with MCA PSV should be used with caution after 36 weeks as its sensitivity for the detection of fetal anaemia decreases.

Qualifying Statements

Qualifying Statements

- These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.
- The Royal College of Obstetricians and Gynaecologists (RCOG) produces guidelines as an educational aid to good clinical practice. They present recognised methods and techniques of clinical practice, based on published evidence, for consideration by obstetricians and gynaecologists and other relevant health professionals. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor or other attendant in the light of clinical data presented by the patient and the diagnostic and treatment options available within the appropriate health services. This means that RCOG Guidelines are unlike protocols or guidelines issued by employers, as they are not intended to be prescriptive directions defining a single course of management. Departure from the local prescriptive protocols or guidelines should be fully documented in the patient's case notes at the time the relevant decision is taken.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Audit Criteria/Indicators

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Bibliographic Source(s)

Royal College of Obstetricians and Gynaecologists (RCOG). The management of women with red cell antibodies during pregnancy. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2014 May. 26 p. (Green-top guideline; no. 65). [42 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2014 May

Guideline Developer(s)

Royal College of Obstetricians and Gynaecologists - Medical Specialty Society

Source(s) of Funding

Royal College of Obstetricians and Gynaecologists

Guideline Committee

Guidelines Committee

Composition of Group That Authored the Guideline

Authors: Professor SK Surendran, FRCOG, Brisbane, Australia; Dr S Allard, MD, FRCP FRCPath, Barts and the London NHS Trust and NHS Blood and Transplant, London; Dr F Regan, FRCP, FRCPath, Imperial College Healthcare NHS Trust and NHS Blood and Transplant, London

Committee Lead Reviewers: Dr P Owen, FRCOG, Glasgow, Scotland; Ms J Elson, FRCOG, Leicester; Dr M Gupta, MRCOG, London

Peer Reviewers: Mr SA Abdel-Fattah, FRCOG, Bristol; Dr ACG Breeze, MRCOG, Kingston upon Thames; Dr JE Brennand, FRCOG, Glasgow; The British Committee for Standards in Haematology (BCSH); British Maternal and Fetal Medicine Society (BMFMS); Dr HM Cameron, FRCOG, Sunderland; Mrs AHD Diyaf, MRCOG, Barnstaple; Dr NJ Engineer, MRCOG, Coventry; Mr OS Eskandar, FRCOG, Barnstaple; NHS Blood and Transplant (NHSBT); Northern Ireland Blood Transfusion Service; Dr AOS Olawo, MRCOG, Rotherham; Mr TG Overton, FRCOG, Bristol; Dr KP Rege, Peterborough City Hospital, Peterborough; RCOG Women's Network; Scottish Clinical Transfusion Advisory Committee (SCTAC) Group; Dr N Singh, MRCOG, Bolton; Mrs P Sinha, FRCOG, St Leonards-on-Sea; UK National Screening Committee; Watch Tower Bible and Tract Society of Britain; Ms A Wijemanne, MRCOG, London

Financial Disclosures/Conflicts of Interest

Conflicts of interest: None declared.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the Royal College of Obstetricians and Gynaecologists (RCOG) Web site .

Availability of Companion Documents

The following are available:

- Development of RCOG Green-top guidelines: policies and processes. Clinical Governance Advice No 1a. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2006 Nov. 6 p. Electronic copies: Available from the Royal College of Obstetricians and Gynaecologists (RCOG) Web site .
- Development of RCOG Green-top guidelines: producing a scope. Clinical Governance Advice No 1b. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2006 Nov. 4 p. Electronic copies: Available from the RCOG Web site .
- Development of RCOG Green-top guidelines: producing a clinical practice guideline. Clinical Governance Advice No 1c. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2006 Nov. 13 p. Electronic copies: Available from the RCOG Web site .
- Development of RCOG Green-top guidelines: consensus methods for adaptation of Green-top guidelines. Clinical Governance Advice No 1d. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2010 Feb. 9 p. Electronic copies: Available from the RCOG Web site .

In addition, suggested auditable topics can be found in Section 14 of the original guideline document .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on July 11, 2014. The information was verified by the guideline developer on July 24, 2014.

Copyright Statement

Disclaimer

NGC Disclaimer

The National Guideline Clearinghouseâ„¢ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria which may be found at http://www.guideline.gov/about/inclusion-criteria.aspx.

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.